



## **Linacotide (Linzess®)**

### **Classification:**

Gastrointestinal Agent—Guanylate Cyclase-C (GC-C) Agonist

### **Pharmacology:**

Mechanism of Action: Linacotide is structurally related to human guanylin and uroguanylin and functions as a guanylate cyclase-C agonist. Both linacotide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation in intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, resulting in increased intestinal fluid and accelerated transit. {1,8}

### **Pharmacokinetics:**

#### **Absorption:**

Linacotide is minimally absorbed with negligible systemic availability following oral administration.

#### **Distribution:**

Given that linacotide plasma concentrations following recommended oral doses are not measurable, linacotide is not expected to be distributed to tissues to any clinically relevant extent.

#### **Metabolism:**

Linacotide is metabolized within the gastrointestinal tract to its principal, active

metabolite by loss of the terminal tyrosine moiety. Both linaclotide and the metabolite are proteolytically degraded within the intestinal lumen to smaller peptides and naturally occurring amino acids.

**Excretion:**

Active peptide recovery in the stool samples of fed and fasted healthy subjects

following administration of linaclotide 290 mcg once daily for seven days averaged

about 5% (fasted) and 3% (fed) and all of it as the active metabolite. {1}

**Indications:**

Chronic idiopathic constipation in adults

Irritable bowel syndrome with constipation {2}

**Dosage and administration:**

Administer orally at least 30 minutes before the first meal of the day on an empty stomach.

Capsules should not be broken, crushed or chewed. For patients with swallowing difficulties, capsules can be opened and administered orally either in applesauce or with water. For patients with a nasogastric or gastric feeding tube, capsules can be opened and sprinkled into 30 mL of room temperature bottled water and administered per tube. Dosage for chronic idiopathic constipation is 145 mcg once daily. A dosage of 72 mcg once daily may be used based on individual presentation or tolerability. Dosage for irritable bowel syndrome with constipation is 290 mcg once daily. {1,2}.

**Contraindications:**

- Patients less than 6 years of age due to the risk of serious dehydration.
- Patients with known or suspected mechanical gastrointestinal obstruction.

**Precautions:**

- Risk of serious dehydration in pediatric patients.
- Diarrhea

**Adverse Reactions:**

- The most common adverse reactions in patients with IBS-C were diarrhea, abdominal pain, flatulence, abdominal distension, viral gastroenteritis and headache.
- The most common adverse reactions with CIC were diarrhea, abdominal pain, flatulence, abdominal distension, upper respiratory infection and sinusitis.

### **Interactions:**

- No known significant reactions.

### **Monitoring:**

- CIC-Frequency of straining during bowel movements; spontaneous bowel movement quality and frequency.
- IBS-C-Abdominal pain, spontaneous bowel movement quality and frequency.

### **HHSC Cost:**

#### **Acquisition cost comparison of GC-C agonists available to HHSC facilities.**

Linaclotide 145 mcg--\$13.18    Linaclotide 290 mcg—\$13.18 Linaclotide 72 mcg--\$14.13

Price comparison: Plecanatide 3mg--\$13.73

Both are once daily dosing.

### **Efficacy:**

The efficacy of linaclotide in the treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) was established in multiple randomized, multicenter,

double-blind, parallel-group, placebo-controlled, dual-dose trials.  
{3,4,5,6,7}

### **Conclusion:**

Linaclotide has been evaluated in a large clinical trial program both for chronic constipation (dose of 145 mcg) and constipation-predominant irritable bowel syndrome (dose of 290 mcg) demonstrating significant and clinically relevant efficacy in improving both broad variety of constipation symptoms as well as abdominal pain and bloating. Diarrhea has been determined as the only relevant adverse effect causing treatment cessation. Linaclotide is one of two guanylate

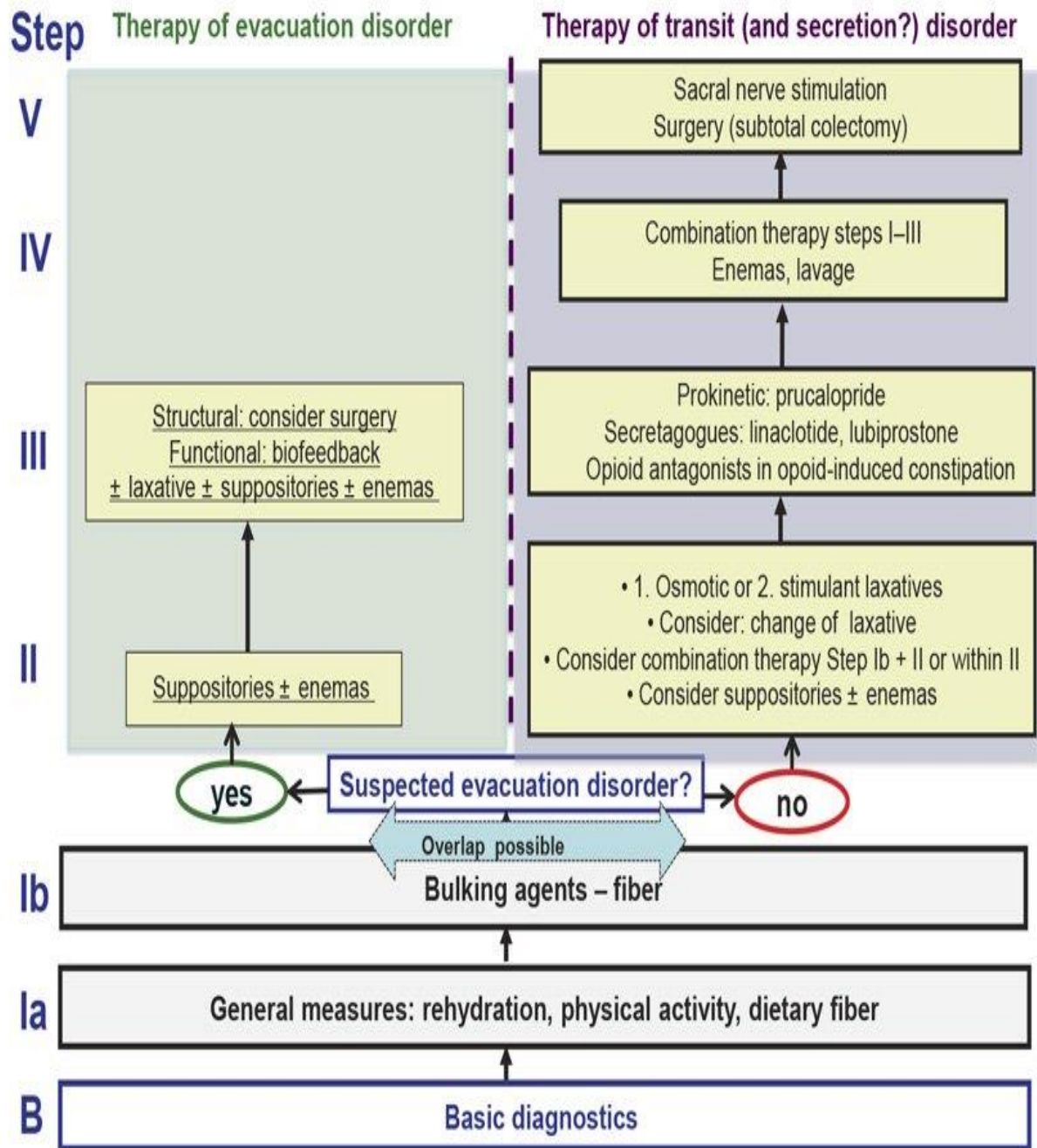
cyclase-C receptor agonists which can be considered after first-line therapies are all exhausted in a stepwise approach for IBS-C and CIC for the patients in our facility. It would be favorable to add linaclotide to our formulary.

References:

1. Product Information: Linzess® capsules. Allergan and Inwood Pharmaceuticals, Inc. Irvine, CA; Cambridge, MA. 2017.
2. Linaclotide Monograph. Lexi-Drugs. Lexi-comp online. Wolters-Kluwer. Accessed 12/27/2018.
3. Alammam, N and Stein, E. Irritable Bowel Syndrome: What Treatments Really Work. Med Clin N Am 103 (2019) 137-152.
4. Lembo, A, Scheier, H et al. Two Randomized Trials of Linaclotide for Chronic Constipation. N Engl J Med 365:6 NEJM.ORG 527-536: 2011.
5. Chey, W, Lembo et al., Linaclotide for Irritable Bowel Syndrome with Constipation: A 26 week, Randomized, Double-blind, Placebo-controlled Trial to Evaluate Efficacy and Safety. [www.amjgastro.com](http://www.amjgastro.com) The American Journal of Gastroenterology. Vol. 107, 1702-1712. 2012.
6. Johnston, J, Kurtz, c et al. Pilot Study on the Effect of Linaclotide in Patients with Chronic Constipation. The American Journal of Gastroenterology. 125-132. 2009.
7. Rao, S, Lembo, A et.al. A 12 week Randomized Controlled Trial with a 4-week Randomized Withdrawal Period to Evaluate the Efficacy and Safety of Linaclotide in Irritable Bowel Syndrome with Constipation. [www.amjgastro.com](http://www.amjgastro.com) . 2012.
8. [www.Uptodate.com](http://www.Uptodate.com) Management of chronic constipation in adults. Accessed 01/07/2019.
9. Andresen, V Medical Therapy of Constipation: Current Standards and Beyond. Visceral Medicine 2018;34:123-127.

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